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(54) Title: DEVICE FOR TOPICAL TREATMENT OF ACNE AND ITS METHOD OF MANUFACTURE

(57) Abstract

The invention provides a device in the form of a patch for the topical application of an anti-acne formulation, comprising a synthetic pressure-sensitive adhesive used as a carrier or associated with a carrier, said carrier having the anti-acne formulation uniformly distributed therein, characterized in that said anti-acne formulation comprises effective amounts of at least two active ingredients from at least two different groups of active ingredients and in that said at least two different groups are selected from the group comprising keratolytic agents, anti-irritant agents, antiseptic agents, antimicrobial agents, hormones, hormone-agonists, hormone-antagonists and other agents suitable for treating acne.

DEVICE FOR TOPICAL TREATMENT OF ACNE AND ITS METHOD OF MANUFACTURE

TECHNICAL FIELD

A delivery device in the form of patch, and method of its manufacture, is provided for the topical treatment of acne and acneiform diseases.

BACKGROUND ART

Acne afflicts 90% of all teenagers but also men and women in their twenties or thirties or may persist throughout adulthood. The process by which acne develops has been described in "New Approaches to Acne Treatment" by W.J.Cunliffe, ed. Martin Dunitz, London, 1989.

Acne vulgaris is a chronic disorder of the pilosebaceous follicles (apparatus) characterized by comedones (blackheads), papules, pustules, cysts, nodules, and often scars, that appear on the most visible areas of the skin particularly on the face, chest, back and occasionally neck, and upper arms.

The pilosebaceous apparatus is largely under the control of endogenous hormones (mainly androgens) which are present in unusually high concentrations in the blood during adolescence and puberty giving rise to an excessive production of sebum. The condition may worsen by a simultaneous increase in the rate of keratinization of the skin's horny layer (the stratum corneum). As the horny cells proliferate, they can form an occlusive plug or comedone which coupled with the increased production of the sebum, represents an ideal medium for the proliferation of the skin resident strains, such as the Gram positive anaerobic bacterium, *Propionibacterium acnes*.

Eventually, the plugged follicles rupture and allow the discharge of their contents causing local swelling and inflammation. The exposed follicles may darken from the deposition of pigment from damaged cells in the deeper layer of skin.

Acne is a multistage condition and in most severe form leads to hospitalization of the patient and extensive discomfort with long term scarring of the skin. There is a need for improved treatments for acne that will effectively prevent the condition developing to its most severe form and that can be used by majority of the sufferers without adverse effects.

At this time there are numerous treatments available for treating acne but each treatment has unfortunate limitations which it would be desirable to overcome. In most part, treatment of acne is by topical formulations in the form of creams, gels, emulsions or lotions which contain selected agents. These agents include hormones or hormone agonists and antagonists (EP A1 0 563 813 and US 5,439,923), antimicrobial agents (US 4,446,145, GB 2,088,717, GB 2,090,135, GB 1,054,124, US 5,409,917), salicylic acid (US 4,514,385, US 4,355,028, EP A1 0 052 705, FR-A 2,581,542, and FR-A 2,607,498). The problems associated with topical treatment of acne with creams, gels, emulsions and lotions include the lack of precision of application and associated lack of control over precise dose at the target site. Application of a cream, gel, emulsion or lotion results in exposure of an area considerably in excess of that covered by lesion thereby exposing normal healthy skin to the anti-acne formulation. For example salicylic acid is an irritant to normal skin over prolonged exposure and particularly in high concentrations.

Oral administration of anti-acne agents is currently provided for severe cases of acne. These are reviewed in "Acne, A Review of Optimum Treatment" by Sykes N.I. and Webster G.F in Drugs 48, 59-70 (1994). Numerous side effects have been described using oral administration of anti-acne drugs. For example, isotretinoin which is a derivative of vitamin A has associated risks of teratogenicity and may be a risk for women of childbearing age. Oral administration of antibiotics suited for treating acne, may induce the appearance of adverse effects which include abdominal cramps,

black tongue, cough, diarrhea, fatigue, irritation of the mouth and other undesirable symptoms.

Salicylic acid in the form of a tacky hydrophilic gel dressing (US 5,258,421) and in combination with pantothenic acid or pantothenic acid derivative in a cleansing pad (PCT WO 93/21899) has been used for treating acne.

In addition, a patch containing cephalosporin has been described in the U.S. Pat. 5,409,917 for the treatment of acne using a method for making nicotine patches. Since the patch was not optimized for the special circumstances associated with acne including optimizing the anti-acne agent content, and placement of the patch at multiple locations on exposed skin such as the face, the patch has not been adopted as a anti-acne formulation delivery modality.

There is a need therefore for methods and devices for treating patients with acne that have minimum adverse effects, have maximum efficacy and may be simple and comfortable to use.

OBJECTIVES OF THE INVENTION

The present invention addresses the need for treating acne and acneiform diseases so as to minimize adverse effects and to maximize efficacy of treatment. The present invention is directed to a topical delivery device, in the form of a patch, having a size and thickness suited for prolonged delivery of anti-acne agents at a selected site characterized as acneiform. The patch contains at least two agents suited for treating acne, in the form of a mixture of compounds.

More precisely, the invention provides a device in the form of a patch for the topical application of an anti-acne formulation, comprising a synthetic pressure-sensitive adhesive used as a carrier or associated with a carrier, said carrier having the anti-acne formulation uniformly distributed therein, characterized in that said anti-acne formulation comprises effective amounts of at least two active ingredients from at least two different groups of active ingredients and in that said at least two different groups are selected from the group comprising keratolytic agents, anti-irritant agents, antiseptic agents,

antimicrobial agents, hormones, hormone-agonists, hormone-antagonists and other agents suitable for treating acne.

In another embodiment, a patch for the treatment of acne and acneiform skin diseases comprises topically acceptable carriers for topical application, such as acrylics, paper, silicones, cellulosics etc.; moisturizers; antioxidants; stabilizers; wherein the patch is capable of delivering an effective amount of anti-acne agents to acneiform skin to be treated (i.e. comedones, pustules, papules).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a side view of a three layered patch for delivering agents for the treatment of acneiform diseases.

Figure 2a is a side view of a four layered patch for delivering agents for the treatment of acneiform diseases.

Figure 2b is a top view of the same patch as in Figure 2a.

Figure 3 shows the stability of the patch of the invention as for salicylic acid and triclosan.

Figure 4a shows the flux of salicylic acid through human stratum corneum as concerns two patches according to the invention and a gel.

Figure 4b is an enlargement of Figure 4a as concerns the two patches of the invention.

DESCRIPTION OF THE INVENTION

The term "topically acceptable carriers", as used herein, means substances substantially lacking toxicity for human tissues.

The term "topical application", as used herein, means directly laying on outer skin.

The term "stable", as used in the specification is defined as possessing a shelf-life that extends for more than several weeks.

The term "effective amount", as used herein, means an amount sufficient to provide an anti-acne effect.

The present invention provides methods and devices for treating patients affected by acne, where the device has been optimized for minimizing adverse effects and for maximizing efficacy and is simple and comfortable to use. The topical treatment of acne and acneiform diseases disclosed herein utilizes a patch to achieve local anti-acne effects that result from the suppression of the proliferation of horny cells and microbes involved in the pathogenicity of acne and reduction in associated inflammation. The patch has been designed so as to effectively deliver anti-acne agents to the stratum corneum (the outermost layer of epidermis, exposed to external environment) and subsequently to penetrate into the pilosebaceous unit (in the dermis) where the acneiform condition originates, while having very limited penetration into the systemic circulation. This is demonstrated by the skin flux permeation study (Example 12 hereafter), which indicates that the amount of salicylic acid that crosses stratum corneum is very small as compared to that of the gel formulation containing 2% of salicylic acid.

In order to ensure that the patch is simple and comfortable to use, a suitable size and thickness of a single patch has been identified. The patch proposed in this invention can be produced in a variety of sizes dependent on the area to be treated (i.e. comedones, papules, pustules). The size of the patch is classified as small being 0.5 to 2 cm^2 and large patch up to 40 cm^2. Typically, the size of the patch is from 0.5 to 1.3 cm^2 and preferably 0.8 cm^2.

The patch of the invention is stable and is capable of safe and effective delivery of the anti-acne formulation. For example, the stored patch containing anti-acne agent may remain effective up to two years such that any chemical changes that may occur during storage, but before the predetermined expiration date, are believed to be non-harmful.

An example of the patch suitable for treating acne is described in Figure 1. In this embodiment, the patch may include a backing film layer 1, a single synthetic pressure-

sensitive adhesive layer 2 and a release liner 3 with the anti-acne formulation contained within the synthetic pressure-sensitive adhesive layer.

In other embodiments, more than one matrix may be positioned between the release liner and the backing layer (see Figures 2a and 2b). According to Figures 2a and 2b and Example 4, a patch is described that includes a backing film layer 1, a synthetic pressure-sensitive peripheral adhesive layer 4, a paper matrix 5, and a release liner 3. The patch may have a paper matrix diameter of 5/8" (inches) (about 1.6 cm) and/or a peripheral adhesive layer diameter of 7/8" (about 2.2 cm).

The backing film layer 1 may be made of plastic or fabric or woven or non-woven materials, porous or occlusive. Porous materials are sometimes used since some of the skin resident strains of the bacteria in the pilosebaceous unit are anaerobic.

The backing film layer can be made of any suitable material such as paper; cellophane; plastic films such as polyethylene, polyester, polyurethane, polyvinyl chloride and polyamide; fabrics and metallic foils, which are impermeable and non-reacting with the anti-acne formulation distributed in the adhesive polymeric matrix. The backing film can be composite or transparent or opaque or fleshtoned or aluminized or a combination thereof, with thickness ranging from 1 to 5 mils (about 25 to 130 μm), typically from 2 to 3.5 mils (about 50 to 90 μm) and preferably 3 mils (about 76 μm), and can be formed from any of CoTran™ 9720 (3M), Saranex ® (Dow Chemicals), Multilam fleshtoned polyester film 1009 (3M), or any other material recognized in the art as having the desired properties.

The patch has an adhesive polymeric matrix 2, which is adjacent to the backing layer and is made of synthetic adhesives such as acrylics, rubber, silicone, cellulosics, paper or other suitable materials that may have pressure sensitive properties and adhere to the skin directly or through a peripheral adhesive. The adhesive polymeric matrix

consists of at least one layer of the adhesive-containing substances and/or other additives. The adhesive polymeric matrix may be composed of more than one layer, but is preferably composed of one layer. The thickness of this adhesive polymeric matrix is in the range of 0.5-30 mils (about 13-760 µm), typically of 0.5-6 mils (13-152 µm), preferably 0.5-2.5 mils (about 13-64 µm) and more preferably 2.5 mils (about 64 µm). Contained within the adhesive polymeric matrix are a mixture of anti-acne agents including any of keratolytics, anti-irritants, antiseptics, antimicrobials, hormones, hormone-agonists, hormone-antagonists and other agents suitable for treating acne, preferably together with solubilizers.

The adhesive polymeric matrix can be made of inert materials which are further biologically and topically acceptable and compatible with the distributed active substances described above.

Preferably, topically acceptable polymers with adhesion properties may be acrylic-based polymers such as the GELVA® series sold by Monsanto and the DURO-TAK® series sold by National Starch; rubber-based polymers such as DURO-TAK® series sold by National Starch; and silicone-based polymers such as BIO-PSA X7-4302 SILICONE PSA sold by Dow Corning.

The said adhesive polymeric matrix can also be made of paper materials, preferably Whatman filter paper, which is adhered onto the skin through a peripheral adhesive layer. The thickness of such an adhesive polymeric matrix is usually 7 mils (about 178 µm).

A release liner 3, is placed against the surface of the adhesive polymeric matrix on the surface opposite to the backing layer. The release liner can be made of materials impermeable to any substance dissolved in the said matrix, which is easily stripped off or released prior to the use. The release liner can be made of materials such as polyvinyl chloride, polyester, polyvinylidene chloride, polystyrene, polyethylene, paper etc. coated or not with an adhesive, but preferably with an easy release silicon formulation.

Preferably the release liner is made of a natural, high impact polystyrene film (grade code: 10106 or 15462) sold by REXAM Release or a siliconized polyester film sold by REXAM Release. The thickness of the release liner can range from 3 to 10 mils (about 76 to 250 μm), or preferably be 10 mils (about 250 μm).

Preferably, the patch has a size in the range of 0.5 to 2 cm^2 and a thickness in the range of 7 to 24 mils (about 178 to 610 μm).

In an embodiment of the invention, a combination of anti-acne agents has been selected to treat acne. These agents include a keratolytic agent, such as salicylic acid, in conjunction with an anti-irritant, an antiseptic, an antimicrobial agent and/or other acne fighting compounds such as for example urea, allantoin, hydroxyquinoline compounds, for delivery via a patch directly to the area to be treated. The presence of an anti-irritant counteracts the local irritation associated with the application of keratolytics to the skin. The antiseptic limits the growth of organisms which cause the acne. Furthermore, the antimicrobial may enhance the overall anti-acne properties of the compositions in moderate or severe stages of the disease. The use of a solubilizer ensures that the active agents in the patch are in form suited for diffusion from the patch to the skin.

Antimicrobials typically used for topical application can be penicillins, cephalosporins, other beta-lactam compounds, aminoglycosides, tetracyclines, erythromycin, antifungal agents, etc. and a combination thereof. Preferably, antimicrobial agents used for topical application onto acneiform skin are erythromycin, tetracycline, clindamycin, cephalosporin.

Antiseptics typically used for topical application onto acneiform skin are triclosan (Irgasan DP 300), phenoxy isopropanol, resorcinol, chlorhexidine, povidone and iodine.

Keratolytic agents typically used for topical application onto acneiform skin are salicylic acid, benzoyl

peroxide, sulphur, retinoic acid and any of a number of fruit acids and alpha hydoxy acids.

Anti-irritants typically used for the topical application onto acneiform skin are α-bisabolol, farnesol, chamomile extract and glycyrrhetinic acid.

Solubilizers used in the anti-acne formulation of the present invention include any of glycerol, propylene glycol, polyalcohols, sorbitol and sorbitol derivatives, preferably sorbitan monooleate.

Compositions of the present invention can also comprise other topically acceptable agents such as solvents, antioxidants, moisturizers etc.

According to a preferred embodiment, the invention provides a device as described above, which comprises, related to the total weight of the carrier and the formulation:

- one or more keratolytic agent(s), each in an amount of 0.1 to 10.0% w/w, preferably of 0.1 to 2.0% w/w and more preferably of 0.6% w/w;
- one or more anti-irritant agent(s),each in an amount of 0.01 to 5.0% w/w, preferably of 0.01 to 3.0% w/w and more preferably of 1.0% w/w;
- one or more antiseptic agent(s), each in an amount of 0.05 to 2.0% w/w, preferably of 0.1 to 1.0% w/w and more preferably of 0.3% w/w; and
- one or more solubilizer(s), each in an amount of 0.1 to 5% w/w, preferably of 1 to 3.0% w/w and more preferably of 2% w/w.

This invention is further illustrated by the examples. Examples are not to be construed as being a limitation on the scope of invention, which scope is defined by the appended claims. The examples are conducted using salicylic acid, as keratolytic agent, in an amount of 0.1 to 2% w/w together with an anti-irritant such as α-bisabolol in 0.01 to 3% w/w, an antiseptic such as triclosan (Irgasan DP 300) in 0.1 to 1% w/w and a solubilizer such as sorbitan monooleate in 0.1 to 5% w/w, having all of them dispensed in

a variety of adhesive polymeric matrices. Controlled delivery is achieved over a period of at least 4 hours, preferably over a period of at least 24 hours and more preferably over a period of at least 8 hours.

Example No. 1

Preparation of polymeric matrix and delivery device in the form of patch.

A composition of the adhesive polymeric matrix used in the preparation of a patch for the topical treatment of acne and acneiform skin diseases contains salicylic acid as keratolytic agent as described in Table 1.

TABLE 1. Composition of the single adhesive delivery system

COMPONENT	QUANTITY % w/w (on a dry basis)
α-Bisabolol [1]	1.0
Irgasan DP 300[2]	0.3
Salicylic acid	0.6
Sorbitan Monooleate	2.0
Gelva® 737	96.1

1. α-Bisabolol is
6-methyl-2-(4-methyl-3-cyclohexen-1-yl)-5-hepten-2-ol

2. Irgasan DP 300 is
2,4, 4'-trichloro-2'-hydroxy diphenyl ether

A method for producing the patch having the above composition is as follows:

Salicylic acid (0.6 g), Irgasan DP 300 (0.3 g), α-bisabolol (1.0 g), sorbitan monooleate (2.0 g) are added to 293.88 g of Gelva® 737 multi polymer resin solution (total

solids content of about 32.7%), and the mixture is stirred at ambient temperature until all the ingredients have dissolved. The mixture is allowed to stand for several minutes so as to remove air bubbles.

The adhesive mixture was formulated into a patch system as follows:

Using an appropriate coating device (square tool steel Multi Clearance Applicator, sold by BYK Gardner) with a 5 or 10 mil (about 130-250 µm) casting gap, a layer of adhesive mixture was coated onto a siliconized polyester film and dried in an oven at 76-78°C for 15-18 minutes. A breathable polyurethane film (Bertek Medfilm 390) was then laminated onto the adhesive film. The system was then delaminated and further laminated on an easy release silicon polystyrene film (REXAM Release). The final thickness of the dried polymeric matrix was, then, 3 to 5 mils (about 76-130 µm).

The multi-layer laminate was then cut to form a patch of circular shape with nominal size of 1 cm^2 (actual size of 0.8 cm^2) and thickness of 7 to 18 mils (about 178-457 µm).

Example No. 2

Preparation of adhesive polymeric matrix

The procedure of *Example 1* is repeated to prepare the adhesive polymeric matrix. The adhesive used in this example is the acrylic-based polymer GELVA® 788. The patch, thus produced, finally has a circular shape of 1 cm^2 and thickness of 8 to 24 mils (about 203-610 µm).

Example No. 3

Preparation of adhesive polymeric matrix containing a mixture of adhesives

The composition of the adhesive polymeric matrix described in this *Example*, in the specified amounts, is presented in Table 2 :

TABLE 2. Composition of the mixed adhesive delivery system

COMPONENT	QUANTITY % w/w (on a dry basis)
α- Bisabolol	1.0
Irgasan DP 300	0.3
Salicylic acid	0.6
Sorbitan Monooleate	2.0
Duro-Tak® 87-2287: Duro-Tak® 87-2353 (1:9 ratio by weight in dry coating)	96.1

A homogeneous mixture is obtained by mixing 18.95 g of Duro-Tak® 87-2287 acrylic solution (total solids content of about 50.7%) and 238.92 g of Duro-Tak® 87-2353 acrylic solution (total solids content of about 36.2%). To this mixture of adhesives, salicylic acid (0.6 g), α-bisabolol (1.0 g), Irgasan DP 300 (0.3 g), sorbitan monooleate (2.0 g) are added and the mixture is stirred at ambient temperature until all the ingredients are dissolved. The mixture is, then, kept aside for several minutes to have the air bubbles completely removed.

The adhesive mixture is formulated into a patch system as follows:

Using an appropriate coating device with a 5 mil (about 130 μm) applicator gap, a layer of adhesive mixture is coated onto a siliconized polyester film. The coating is left to dry in an oven at 80°C for 17 minutes and then laminated using an occlusive polyethylene film.

The process ends with cutting the multi-layer laminate to a patch of circular shape, size of 1 cm^2, and thickness of 7.5 to 20 mils (about 190-500 μm) which is

finally pouched in a flexible, pouching laminate film composed of paper, low density polyethylene, aluminium and Surlyn®.

Example No. 4

Preparation of a delivery device in the form of patch containing a plain adhesive layer and a polymeric matrix with and without adhesive properties

In this *Example*, substances such as antimicrobials, antiseptics, keratolytics, anti-irritants and solubilizers are distributed in a polymeric matrix in which the polymers may or may not have adhesive properties.

The procedure of preparing this patch is presented as follows:

To 10 g ethanol AR, salicylic acid (0.1 g), α-bisabolol (0.1 g), Irgasan DP 300 (0.03 g) and sorbitan monooleate (0.2 g) are added and the mixture is stirred until all the ingredients are dissolved.

Pieces of Whatman filter paper are impregnated with 3 ml of the above ethanolic solution and left to drain at ambient temperature. The impregnated paper pieces are, then, dried in an oven at 40°C for 5 minutes and finally cut into a desirable size and shape (i.e. circular shape of 5/8" diameter or area of 5 cm^2).

Siliconized polyester films are coated with a plain, acrylic-based adhesive such as Duro-Tak® 87-2287 or Duro-Tak® 87-2353. The bilayer system is dried in an oven at 78-80°C for 15 minutes and, then, laminated with a polyethylene film such as CoTran™ 9720. The whole system is cut into a desirable size and shape (i.e. circular shape of 7/8" diameter or area of 7 cm^2).

The polyester film is removed and, onto exposed laminate, the impregnated paper is placed in a co-centric order. Finally the multi-layer system is coated on a polystyrene film, which can be scored on the backside (see Figures 2a and 2b).

Example No.5

Preparation of a delivery device in the form of patch as in Example No 4 containing an additional adhesive layer.

The procedure of *Example 4* is repeated to prepare a patch, in which the exposed laminate is coated on a polystyrene film coated completely or partially with a plain adhesive.

Example No. 6

Stability of the produced patch

The patch proposed in the present invention will remain stable for two years. Methods such as composite assay for salicylic acid and physical tests (such as 90° dynamic adhesive strength peel test for matrix patch from stainless steel plate as in "Test Methods for Pressure Sensitive Adhesive Tape" developed by The Technical Committee of the Pressure Sensitive Tape Council, 11th Edition) are used to determine its stability over this time.

Furthermore the stability of the proposed patch was examined under ambient conditions. The results expressed as % amount of salicylic acid and triclosan detected in the patch over the time are presented in Figure 3.

Example No. 7

Patch depletion analysis

The patch produced is designed to release its content at 4, 6, 10, and up to 24 hours after application. To determine the rate and extent of the release for salicylic acid from the patch, a patch depletion analysis is performed.

Example No. 8

Primary Dermal Irritation Study

A Primary Dermal Irritation Study, in compliance with the FDA Requirements per 21 CFR 58, was performed using patches containing salicylic acid, as disclosed in preferred embodiments, in order to identify the potential irritation or corrosive effects that result from the exposure of rabbit skin to the test material.

The fur of six healthy New Zealand rabbits was clipped as close to the skin as possible at the test site twenty-four hours prior to the application of the test material.

The test material was applied to both intact and abraded skin, and each test area was covered with an 1 inch square gauze patch hold in place with non-irritating tape. The skin exposed to the test material for a period of twenty-four hours and examinations of the animals for signs of erythema, edema, and any lesions or other toxic effects were made at thirty to sixty min after patch removal and, then, at seventy-two hours.

The study showed that the patches produced a very slight erythema with some flaking skin at some test sites but no edema. In addition, no other toxic effects were observed during the study.

The Primary Irritation Score as estimated was 0.54 which indicates that the test material is not considered to be a primary skin irritant as defined in 16 CFR 1500.3 (c) (4).

Example No. 9

Delayed Contact Hypersensitivity test - Modified Buehler sensitization test.

A Delayed Contact Hypersensitivity test, in compliance with the FDA Requirements per 9 CFR 2.31, was performed using patches containing salicylic acid, as disclosed in the preferred embodiments, in order to determine the capacity of the test substance to induce a systemic hypersensitivity response.

The experimental procedure consisted of two phases:

1. Induction phase

One group of 20 guinea pigs was exposed to the test material patch and one group of 10 guinea pigs was exposed to Dinitrochlorobenzene (DNCB), a known sensitizer. The day before dosing, the animals were clipped free of hair, as close to the skin as possible, using electric clippers.

The test material patch was applied to the clipped area of each of the 20 guinea pigs and held in place with a non-irritant tape. The patches were left in place for 6 hours and then removed. The test sites were scored for erythema at 24 and 48 hours post application. This procedure was repeated at the same site once a week for the next two weeks for a total of three 6-hour exposures. After the last patch application the animals remained untreated for approximately two weeks.

To the positive control group of 10 guinea pigs, a solution of 0.75% of DNCB in 50 % ethanol was applied and scored as previously described.

In the following tables the individual scores for the test material patch and the positive control are presented.

TABLE 3. Individual animal scores for the test material.

Erythema

	Week 1		Week 2		Week 3	
Animal	24 h	48 h	24 h	48 h	24 h	48 h
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
5	0	0	0	0	0	0
6	0	0	0	0	0	0
7	0	0	0	0	0	0
8	0	0	0	0	0	0
9	0	0	0	0	0	0
10	0	0	0	0	0	0
11	0	0	0	0	0	0
12	0	0	0	0	0	0
13	0	0	0	0	0	0
14	0	0	0	0	0	0
15	0.5	0	0	0	0	0
16	0	0	0	0	0	0
17	0	0	0	0	0	0
18	0	0	0	0	0	0
19	0	0	0	0	0	0
20	0	0	0	0	0	0

There was no erythema noted for the test material patch during the three induction phases.

TABLE 4. Individual animal scores for the positive control. Erythema

	Week 1		Week 2		Week 3	
Animal	24 h	48 h	24 h	48 h	24 h	48 h
1	0.5	0	0.5	0	2	1
2	1	0.5	1	1	2	1
3	1	0	1	0.5	1	1
4	0.5	0	1	0.5	2	2
5	1	0.5	0.5	0	1	1
6	1	0	1	0.5	2	1
7	0.5	0	1	1	2	1
8	1	0	1	1	2	1
9	1	0.5	1	1	1	1
10	1	0.5	1	0.5	2	1

During this test, animals showed from no to faint and faint confluent erythema.

2. Challenge phase

After the two week rest, the test group and the positive control group were challenged on naive sites. The test material was applied to the test group and the DNCB to the positive control group. The procedure employed was as described above, except skin evaluations were made at 24, 48 and 72 hours post application. The results are presented in the following tables.

TABLE 5. Individual animal scores for the test material. Erythema

Animal	24 h	48 h	72 h
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0.5	0	0
16	0	0	0
17	0	0	0
18	0	0	0
19	0	0	0
20	0	0	0

During the challenge phase, no erythema was noted in the test or naive test material group at any point.

TABLE 6. Individual animal scores for the positive control. Erythema

Animal	24 h	48 h	72 h
1	1	0.5	0.5
2	1	0.5	0.5
3	1	1	0.5
4	1	0.5	0.5
5	1	1	0.5
6	1	0.5	0
7	1	0.5	0.5
8	2	1	0.5
9	2	1	0.5
10	1	1	0.5

During this test, animals showed from no to faint and faint confluent erythema.

Example No 10

Repeated Insult Patch Test for Contact Sensitization and Photosensitization.

The purpose of this study was to determine the cutaneous and contact sensitization and photosensitization in human volunteers of the patch containing salicylic acid as described in the preferred embodiments of the present invention, in order to claim the "hypoallergenicity" of the product.

Forty (40) healthy volunteers of both sexes, aged 20-55 years old, were included in the study.

1. Induction phase

In this part, repeat insult patch tests in combination with maximization test were used. On intact skin of the upper back of the forty volunteers, a 1% solution of sodium lauryl sulfate was applied. The test product was, then, applied and held with a non-irritant tape. The test material was left on, for 48 hours and the site was read 30 minutes after the removal of the patch. A new patch was then

reapplied to the same site. New patches were applied 3 times per week and assessments were carried out at 48 hour post removal. Repeated application of the patches using this method was continued for three weeks (total ten applications).

Additional patche tests were used to determine the contact photosensitization of the patch. During the induction phase and in parallel with the repeat patch tests, the patch tests sited were irradiated on five occasions with a solar stimulator or UVA (5 Joules) after removal of five repeated patches (serial). The phototoxic potential of the test patch was evaluated on hour, 6 and 24 hours after a single treatment.

2. Challenge phase

After the end of the three week period a rest period of fifteen days followed. At the end of the rest period patch tests were performed as follows:

The sodium lauryl sulfate solution was first applied to the back followed by the test material patch. In the challenge test, the patch was removed at 48 hours post application and assessments were carried out at 24, 48 and 72 hours post application. During the challenge phase a second test patch was performed at another site and after its removal the site was irradiated with UVA (5 Joules). Readings were performed at 72 and 96 hours post application.

The assessments for both phases were carried out by the same investigator and under the same conditions. Scoring was based on the standard ICDRG scale. The results were negative for both phases and thus the test patch can be considered as "Hypoallergenic" and "Dermatological Tested".

Example No 11

Repeated Irritation Test in Humans.

The purpose of this study was to provide a quick and simple indication of the potential irritancy for the test patch. Because of the lower sensitivity of human skin to irritants, versus animal model, testing in man is generally performed by repetive application of the test patch.

The study involved 20 volunteers, male or female (15-50 years old), whose upper backs were free from any skin problems.

The test material patch was initially applied in the upper back of the volunteer for 24 hours, held with a non-irritant Scanpor tape, and then removed. One hour upon removal, the skin site was gently wiped with a moist wool ball and graded. The test material application was repeated at the same site, 24 hours later. The test material application continued for 20 days (total of 10 applications with a rest period over the weekends).

The results showed no sight of erythema, edema or exudation induced by the test patch and thus the product can be considerd as "Non irritant".

Example No 12

Permeability of the anti-acne patches.

To evaluate the local effect of the anti-acne patches according to the invention, the transdermal absorption (flux) of the salicylic acid from the adhesive matrix of the invention was determined *in vitro* by using human cadaver skin, according to the procedure described by Franz T., in Percutaneous absorption on the relevance of the *in vitro* data, J. Invest. Derm. 64, 190-195, 1975.

For *in vitro* flux studies, the stratum corneum of human cadaver skin was used. Using fresh, post-mortem skin samples, the stratum corneum was separated from the skin by the technique described by Kligman, A. M. Et al in Preparation of the isolated sheets of the human stratum corneum, Arch. Derm. 88, 702, 1963.

A comparative study of skin flux determination (expressed as cumulative amount of salicylic acid permeation per unit of area at any time) between the anti-acne patch of the invention (**Patch 1**), the same patch but having an adhesive matrix of double thickness (**Patch 2**) and a reference gel formulation containing 2% of salicylic acid (**Gel**) is presented in Figure 4 [Fig. 4a and Fig. 4b].

The results showed a very limited penetration for the anti-acne patch of both adhesive matrix thickness as compared to that of the reference gel formulation, assuring thus the local effect of the proposed anti-acne patch..

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country.

For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the words "comprise" and "comprises" have a corresponding meaning.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A device in the form of a patch for the topical application of an anti-acne formulation, including a synthetic pressure-sensitive adhesive used as a carrier or associated with a carrier, said carrier having the anti-acne formulation uniformly distributed therein, wherein the anti-acne formulation includes effective amounts of at least two active ingredients selected from at least two different groups of active ingredients in which the at least two different groups include keratolytic agents, anti-irritant agents, antiseptic agents, antimicrobial agents, hormones, hormone-agonists or hormone-antagonists.

2. A device according to claim 1, in which said anti-acne formulation further includes one or more solubiliser(s).

3. A device according to claim 1 or 2, further including one or more acceptable carrier(s) for topical application.

4. A device according to any one of claims 1 to 3, which includes, related to the total weight of the carrier and the formulation:

- one or more keratolytic agent(s), each in an amount of 0.1 to 10.0% w/w;

5. A device according to claim 4 in which the one or more keratolytic agent is present in an amount of 0.1 to 2.0% w/w.

6. A device according to claim 4 in which the one or more keratolytic agent is present in an amount of 0.6% w/w.

7. A device according to any one of claims 1 to 6 in which the one or more anti-irritant agent is present in an amount of 0.1 to 3.0% w/w.

8. A device according to any one of claims 4 to 7 in which the one or more anti-irritant agent is present in an amount of 1.0% w/w.

9. A device according to any one of claims 4 to 8 in which the one or more antiseptic agent is present in an

amount of 0.1 to 1.0% w/w.

10. A device according to claim 9 in which the one or more antiseptic agent is present in an amount of 0.3% w/w.

11. A device according to any one of claims 4 to 10 in which the one or more solubiliser is present in an amount of 1 to 3.0% w/w.

12. A device according to claim 11 in which the one or more solubiliser is present in an amount of 2% w/w.

13. A device according to any one of claims 1 to 12, wherein the synthetic adhesive is provided with a backing film layer on a first side, and with a release liner adhered on the opposite side, which opposite side will enter into contact with the skin surface upon use of the device.

14. A device according to claim 13, wherein the backing film is occlusive.

15. A device according to claim 13, wherein the backing film is breathable.

16. A device according to any one of claims 1 to 15, wherein the synthetic carrier is formed in multiple layers.

17. A device according to any one of claims 1 to 16, wherein the synthetic carrier is an adhesive polymeric matrix.

18. A device according to claim 17, wherein the adhesive polymeric matrix is formed from one or more adhesive polymers.

19. A device according to claim 17 or 18, wherein the adhesive polymeric matrix is made of one or more polymers selected from acrylic-based polymers, rubber-based polymers or silicone-based polymers and being topically, acceptable and provided with adhesion properties.

20. A device according to any one of claims 1 to 19, wherein the keratolytic agent is salicylic acid, benzoyl peroxide, sulphur, retinoic acid or any of a number of fruit acids or alpha hydroxy acids.

21. A device according to any one of claims 1 to 20, wherein the anti-irritant agent is α-bisabolol, farnesol,

glycyrrhetinic acid or chamomile extract.

22. A device according to any one of claims 1 to 21, wherein the antiseptic agent is triclosan, phenoxy isopropranol, resorcinol, chlorhexidine, povidone or iodine.

23. A device according to any one of claims 2 to 22, wherein the solubiliser is glycerol, propylene, glycol, polyalcohols, sorbitol or sorbitol derivatives.

24. A device according to claim 23 wherein in which the sorbitol derivative is sorbitan monooleate.

25. A device according to any one of claims 1 to 24, further including an anti-microbial agent.

26. A device according to claim 25 in which the anti-microbial agent is erythromycin, tetracycline, cephalosporin or clindamycin.

27. A device according to any one of claims 1 to 26, providing prolonged delivery of the formulation for at least 4 hours.

28. A device according to claim 27 providing prolonged delivery of the formulation for at least 24 hours.

29. A device according to claim 28 providing prolonged delivery of the formulation for at least 48 hours.

30. A device according to any one of claims 1 to 29, which has a size in the range of 0.5 to 2 cm^2 and a thickness in the range of 7 to 24 mils (about 178 to 610μm).

31. A device according to any one of claims 1 to 30, wherein the keratolytic agent is salicylic acid.

32. A device according to claim 31, wherein the effective amount of salicylic acid is 0.6% w/w.

33. A device according to any one of claims 1 to 32, wherein the antiseptic is triclosan.

34. A device according to any one of claims 1 to 33, wherein the anti-irritant is α-bisabolol.

35. A device according to any one of claims 1 to 34,

wherein the solubiliser is sorbitan monooleate.

36. A device according to any one of claims 1 to 35, wherein the anti-acne formulation is uniformly distributed in a paper associated with the synthetic adhesive.

37. A method for manufacturing the device of any one of claims 1 to 36, including:

(a) mixing a single adhesive or a mixture of adhesives with an anti-acne formulation so as to form a blend; and

(b) laminating the blend on a first side with a release liner and on a second side with a backing film.

38. A device in the form of a patch for the topical application of an anti-acne formulation substantially as herein before described with reference to the accompanying drawings.

39. A device in the form of a patch for the topical application of an anti-acne formulation substantially as herein before described with reference to any one of the foregoing examples apart from example 12.

40. A method for manufacturing the device of any one of claims 1 to 36 substantially as herein before described with reference to the accompanying drawings.

41. A method for manufacturing the device of any one of claims 1 to 36 substantially as herein before described with reference to any one of the foregoing examples apart from example 12.

Dated this 30th day of January 2001

LAVIPHARM S.A.

By their Patent Attorneys

GRIFFITH HACK

Fellows Institute of Patent and

Trade Mark Attorneys of Australia

Fig.1

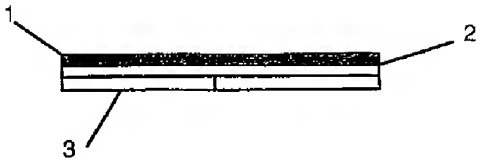


Fig.2a

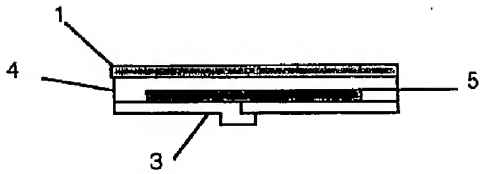


Fig.2b

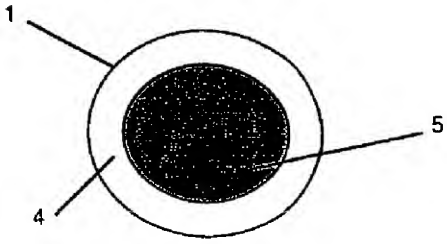


Fig.3

Stability of acne patch as for Salicylic acid and Triclosan

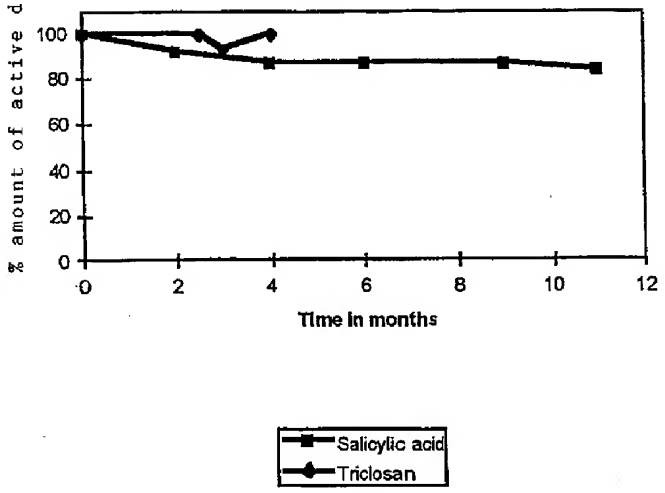


Fig.4a

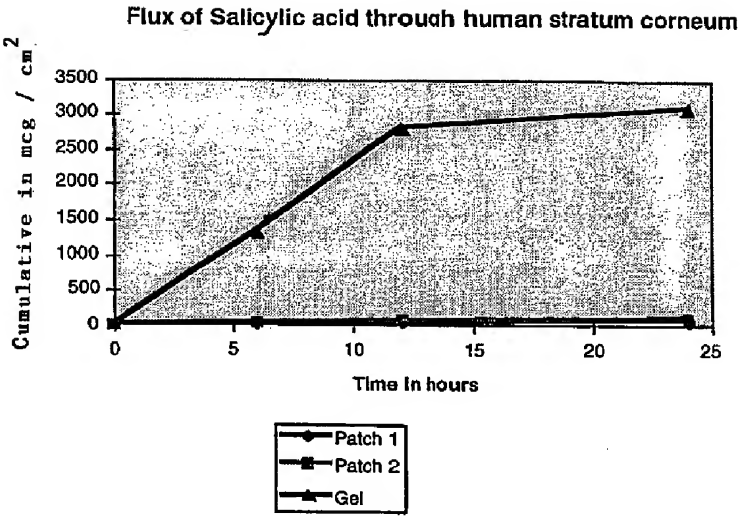
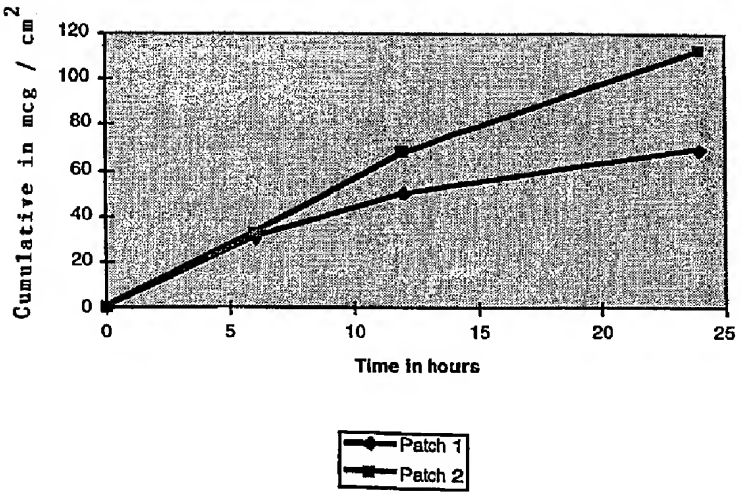

Flux of Salicylic acid through human stratum corneum
Cumulative in mcg / cm 2
3500
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
Time in hours
Patch 1
Patch 2
Gel

Fig. 4b


Cumulative in mcg / cm 2
120
100
80
60
40
20
0
0
5
10
15
20
25
Time in hours
Patch 1
Patch 2